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Dose-Intensive Therapy for Extensive-Stage Small Cell Lung Cancer and Extrapulmonary Small Cell Carcinoma: Long-term Outcome

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ABSTRACT

Treatment for extensive-stage small cell lung cancer (ES SCLC) or extrapulmonary small cell carcinoma (EPSC) is typically palliative. We set out to determine progression-free survival (PFS) and overall long-term survival of ES SCLC and EPSC patients, physiologically aged ≤60 years, responding to first-line chemotherapy followed by high-dose combination alkylating agents with hematologic stem cell support. Patients in first-line chemotherapy response underwent stem cell collection (marrow, peripheral blood progenitor cells, or both) followed by high-dose therapy with 1 of 2 regimens: CBP (cyclophosphamide, cisplatin, and carmustine) or ICE (ifosfamide, carboplatin, and etoposide) with or without etanidazole. Involved-field radiotherapy was given to selected patients with oligometastatic disease distributed in sites allowing for reasonable radiation ports, and prophylactic cranial radiotherapy was given upon recovery to patients in complete response (CR) or near-CR. A total of 36 patients were treated. Of 29 patients with ES SCLC, 6 (21%) had achieved CR, 18 near-CR, and 5 partial response prior to high-dose therapy. Of 7 patients with EPSC, 3 (43%) had achieved CR, 3 had achieved near-CR, and 1 had progression of disease prior to high-dose therapy. Thirteen ES SCLC patients received high-dose CBP. Of the remaining 23 patients with SCLC or EPSC, 17 were treated with ICE and 6 with ICE plus etanidazole, a hypoxic cell sensitizer. Treatment-related mortality was 11% (4 of 36 patients). For all patients, the median event-free survival (EFS) was 5 months. The 2- and 5-year survivals after intensification were 12% (95% confidence interval [CI], 5%-31%) and 9% (95% CI, 3%-27%), respectively. Of the 30 patients in or near CR prior to high-dose therapy, 5 remain continuously progression-free (2 ES SCLC, 3 EPSC) for a median of 55 months (range, 1-96 months) after high-dose therapy. By multivariate analysis, factors associated with more favorable EFS were the use of a more aggressive induction regimen (ICE), and the EPSC histology. These factors were also associated with more favorable overall survival. Other factors associated with more favorable overall survival were the use of short induction therapy (≤4 cycles) and younger age (<50 years). Except for high-dose ICE with etanidazole, the use of high-dose systemic therapy in ES SCLC and EPSC was associated with low treatment-related morbidity and mortality over the past 5 years. Late complications were infrequent, and most patients returned to full-time work and activity, barring disease recurrence. Nonetheless, few patients with ES SCLC have progression-free long-term survival. We conclude that high-dose therapy is not indicated as an approach for ES SCLC, except as part of an investigative trial. Conversely, 3 of the 7 patients with EPSC remain relapse-free (range, 1-96 months), warranting further phase II evaluation of this approach in this population.

KEY WORDS

Small cell lung cancer • Hematopoietic stem cell support • Phase II

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INTRODUCTION: RATIONALE FOR DOSE-INTENSIVE THERAPY IN SMALL CELL LUNG CANCERS

Tobacco-related respiratory cancers are the leading preventable cause of death from cancer in both men and women [1]. Approximately 30,000 new cases of small cell lung cancers (SCLC) arise each year in the United States, of which two thirds are metastatic (extensive-stage [ES] SCLC). Extrapulmonary small cell carcinomas (EPSC) arise in numerous organs, typically from respiratory, gastrointestinal, or gynecologic tracts, and are relatively rare. They are included in this report because their biologic behavior and response to therapy are quite similar to that of ES SCLC [2]. Treatment is palliative and usually consists of 4 to 6 cycles of combination chemotherapy such as etoposide and platinum (EP) or carboplatin (CbE) [3]. Overall response rates are about 60% (13%-25% complete responses [CR]), but practically all patients will relapse within months. Expected median survival is 10 to 14 months from initiation of therapy. Only about 5% of patients remain alive by 2 years, and fewer than 2% survive 5 years [4].

The utility of dose or dose intensity of chemotherapy to enhance response and survival remains controversial. Standard combination chemotherapy is superior to low-dose treatment; however, no clear benefit has been documented with modest or high dose escalation [5-12]. In the only randomized trial comparing transplantation to conventional therapy, Humblet et al. [13] treated 101 SCLC patients with 5 cycles of chemotherapy but without thoracic radiotherapy. Forty-five (13 ES SCLC) were eligible for randomization to 1 further cycle of either high-dose or conventional-dose therapy with cyclophosphamide, etoposide, and carmustine (BCNU) [13]. Although a clear dose-response relationship was demonstrated, a dose-survival relationship was blunted by an 18% toxic death rate on the autologous bone marrow transplantation arm, which lacked consolidative thoracic radiotherapy.

The safety of high-dose therapy has improved markedly over the past 5 to 10 years, particularly with the advent of peripheral blood progenitor cell (PBPC) support. Thus the strategies of intensifying induction therapy, dose-intense chest radiotherapy, and dose-intensive combination therapies with stem cell support are now much more feasible even in a more fragile elderly population such as SCLC patients.

We present the long-term outcomes of 36 patients with ES SCLC or EPSC in partial response (PR) or CR to conventional dose induction chemotherapy who subsequently received dose-intensive combination alkylating-agent therapy with hematopoietic stem cell support followed by prophylactic cranial radiotherapy. Both high-dose regimens, CBP and ICE, have known activity against SCLC [14-16].

METHODS

Eligibility

Patients physiologically younger than age 60 years (ie, patients with a performance status of 0-1 and limited comorbidity older than age 60 years accepted on a case-by-case basis) with extensive-stage histologically documented SCLC or EPSC, in continued response to first-line conventional-dose induction chemotherapy, were eligible for enrollment in this series of sequential studies. After maximal response from induction chemotherapy (generally approximately 4 cycles), restaging studies were carried out including head, chest, and upper abdominal computerized tomography scans; bone scan; bilateral marrow aspirates and biopsies; and eligibility laboratory tests. Eligibility was specific to each study, but in general, prior to hematopoietic stem cell collection, included a Zubrod performance status of 0 to 1, leukocyte count ≥3000/μL, platelet count ≥100,000/μL, creatinine level ≤1.5 × normal, creatinine clearance ≥60 mL/min, serum SGOT (aspartate aminotransferase [AST]) level and bilirubin level ≤1.5 × normal, forced vital capacity (FVC) and carbon monoxide diffusing capacity (DLCO) ≥60% of predicted (corrected for hemoglobin), and left ventricular ejection fraction (LVEF) ≥45%. Diagnostic pathology or cytology was reviewed by the Brigham and Women's Hospital Department of Pathology. Written informed consent was obtained and the study was conducted according to the guidelines of the Dana-Farber Cancer Institute and Beth Israel Deaconess Medical Center institutional review boards.

Treatment

The treatment schemas and regimens are outlined in Figure 1.

Induction Therapy. Patients were referred after achieving PR, near-CR, or CR to combination chemotherapy.

Hematopoietic Stem Cell Collection. Marrow was harvested under general anesthesia and cryopreserved as previously described [17]. PBPCs were collected by leukapheresis and cryopreserved after mobilization with granulocyte- or granulocyte-macrophage colony-stimulating factor (GM-CSF) according to standard methods [17]. Patients were eligible for participation on several sequential supportive care protocols. Thus, hematopoietic support consisted of marrow alone in 8 patients, marrow augmented by G-CSF– or GM-CSF–mobilized PBPCs in 13 patients, chemotherapy/G-CSF–mobilized PBPCs alone in 13 patients, and cyclophosphamide/G-CSF–mobilized CD34-selected PBPCs (CellPro Ceprate column; CellPro Inc, Bothell, WA) in 2 patients.

High-Dose Therapy. The high-dose "intensification" chemotherapy regimen CBP consisted of cyclophosphamide (1875 mg/m^2 as a 2-hour infusion daily for 3 days), cisplatin (55 mg/m^2 per day by continuous infusion over 72 hours), and BCNU (60 mg/m^2 per dose given as a 1-hour infusion twice daily for 4 days). The total doses were 5625, 165, and 480 mg/m^2, respectively. High-dose intensification chemotherapy regimen ICE consisted of ifosfamide (4000 mg/m^2 per day × 4 days), carboplatin (450 mg/m^2 per day × 4 days), and etoposide (300 mg/m^2 per day × 4 days), all given by continuous intravenous infusion with mesna uroprotection. The total doses were 16000, 1800, and 1200 mg/m^2, respectively [18]. Eight patients received ICE plus etanidazole [19]. Hematopoietic stem cells were reinfused (day 0) 48 to 72 hours after completion of chemotherapy.

Radiotherapy. Involved-field radiotherapy (varied doses) for patients with oligometastatic disease (3 or fewer metastatic sites of disease) and prophylactic cranial radiotherapy (30 Gy in 15 fractions) for complete responders were administered after complete recovery from the acute side effects of intensification chemotherapy. Patients who had received radiotherapy prior to intensification were eligible for protocol.

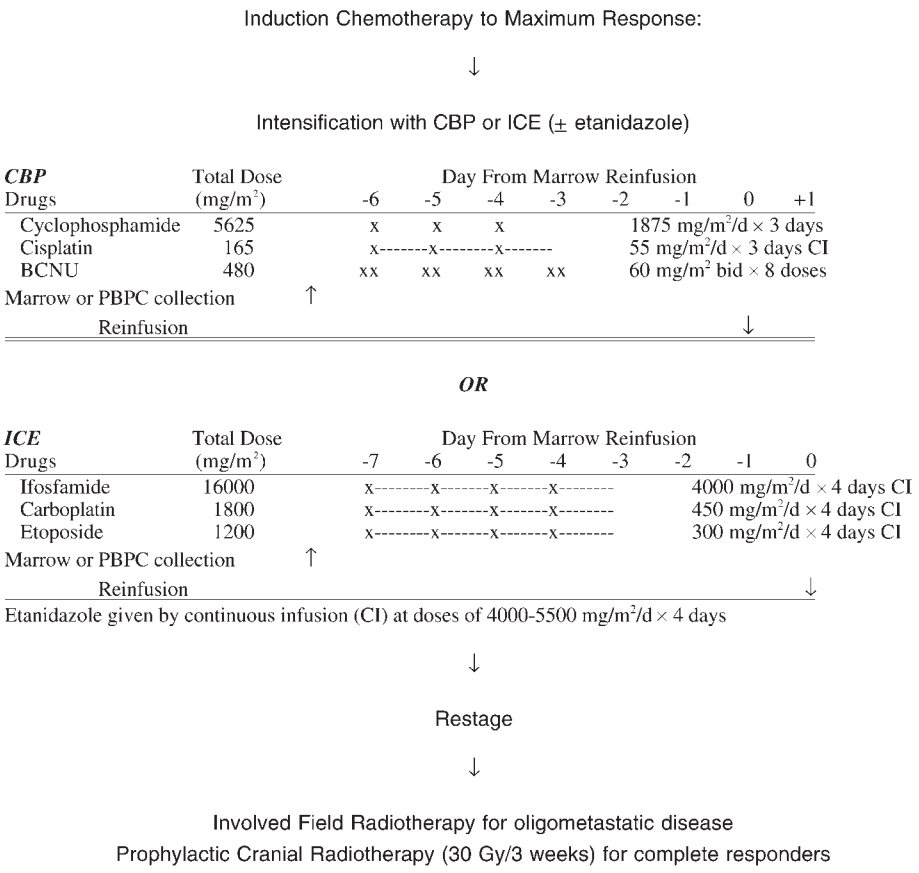

Figure 1. Treatment schemas and regimens.

Statistical Methods

Standard response criteria were used. CR required total disappearance of tumor for at least 4 weeks and/or absence of tumor in surgical biopsy specimens with persistent abnormalities. Near-CR was defined as >90% tumor reduction for at least 4 weeks with persistent radiographic abnormalities such as residual parenchymal scarring without nodular characteristic, residual pleural or pericardial thickening, or residual mediastinal adenopathy less than 1.5 cm in greatest diameter. PR required 50% to 90% reduction for at least 4 weeks of the product of perpendicular diameters of all measurable lesions. Stable disease was defined as <50% reduction or <25% increase of the same parameters for ≥8 weeks, and progression of disease (PD) required a ≥25% increase in lesions or the appearance of any new lesions. Time to failure was calculated from day 0 of intensification (unmaintained by further systemic therapy) to the documentation of progression or death from any cause. Survival was calculated from day 0 of intensification to the documentation of death from any cause. Time to failure and survival were estimated by the Kaplan-Meier method [20]. Confidence intervals (CI) were constructed around the Kaplan-Meier estimates using Greenwood's variance formula [21]. Univariate comparisons of these endpoints between patient groups based on pretransplantation characteristics, such as induction response, were made using the log-rank test [22]. Multiple factors were simultaneously assessed using proportional hazards regression [23]. However, statistical power is limited because of small sample sizes. The number of days to granulocyte count > 500/μL, to platelet count >20,000/μL, and to red blood cell (RBC)-transfusion independence were compared between patients treated with and without PBPCs using a generalized Wilcoxon statistic [21]. This statistic weights early differences in the time to a particular event more heavily than late differences. When examining the time to engraftment, early differences are clinically more important. This test reduces to the Wilcoxon Rank Sum test in the absence of censoring.

RESULTS

Patient Characteristics

From July 1987 to May 2000, 29 patients with ES SCLC and 7 patients with EPSC were enrolled (Table 1). The patients were selected for PR or better to first-line therapy, lack of significant active comorbid disease, and ability to obtain financial coverage and were referred from all over the United States. Median age was 49 years (range, 26-61 years); 81% had a performance status of 0 at initiation of high-dose therapy, and 53% were men. Except for chronic bronchitis or emphysema, most patients had no active comorbid disease. Three patients presented with syndromes of inappropriate antidiuretic hormone. Of the 7 patients with EPSC, sites of presentation included respiratory tract in 4 and gastrointestinal or gynecologic in 3. Patients had a median of 3 organs/sites of disease involved (range, 1-9 organs/sites).

Table 1. *Characteristics of 36 Patients with Extensive-Stage SCLC or Extrapulmonary Small Cell Carcinoma**

Characteristic	No. of Patients	(Range)%
All patients	36	
ES SCLC	29	
EPSC†	7	
Median age	49	(26-61)
Male/female	19/17	53/47
Median pack-years smoking	39	(0-140)
SCLC	47.5	(20-140)
EPSC	0	(0-20)
Prognostic factors prior to induction therapy		
Performance status 0 at diagnosis	15	42
>5% weight loss within 6 months prior to diagnosis	8	22
Paraneoplastic syndrome	3	8
Abnormal LDH >600 (n = 24)	15	63
CEA ≥5 prior to therapy (n = 15)	8	53
TNM stage (SCLC only)		
T1N0M1	1	3
T1-3N2M1	12	41
Tx-2N3M1	3	10
T3N3M1	5	17
T4N2-3M1	8	28
Sites of metastatic disease		
No. of organs involved	3	(2-9)
Visceral (BM, Br, L, Sp, GI, A)	23	64
Median no. of induction cycles	5	(2-10)
Months from diagnosis to high-dose therapy	6	(2-10)
Best response to induction		
Complete response	9	25
Near-complete response (VGPR, PR)†	21	58
Partial response	5	14
Progressive disease	1	3

*LDH indicates lactate dehydrogenase; CEA, carcinoembryonic antigen; TNM, (primary) tumor, (regional lymph) node, (remote) metastases (classification, staging); Br, brain; L, liver; Sp, spleen; GI, gastrointestinal tract; A, adrenal; VGPR, very good partial response.

†EPSC primary sites (residual disease at induction): esophageal (liver, nodes), parotid (cervical nodes), sinus (inoperable ethmoid/maxillary sinus), tongue (primary, cervical and supraclavicular nodes), colon (liver), gynecologic (liver, peritoneum, abdominal wall, spleen), pelvis (pelvic organs, nodes).

Treatment

A median of 5 cycles of induction chemotherapy was given (range, 2-10 cycles). Because most patients were referred after initiation of chemotherapy, varied regimens were given. Three patients received non–platinum-containing induction (doxorubicin, vincristine, etoposide, and midcycle methotrexate [MAVE] or cyclophosphamide, doxorubicin, and etoposide [CAE]), and 33 received etoposide and either cisplatin or carboplatin (PE or CbE) regimen; 11 of these patients received ifosfamide as part of their therapy. Nine patients achieved CR, 21 near-CR, 5 PR, and 1 PD to induction therapy (prior to high-dose therapy).

Involved-field radiotherapy to the primary lesion, hilum, mediastinum, and bilateral supraclavicular areas was administered in 15 patients. The median doses to the extended and involved fields were 41.4 Gy (range, 30-56 Gy) and 50.2 Gy (range, 43-64.8 Gy), respectively. Radiotherapy was also given to bony sites in 5 patients, the brain in 4 patients, and the adrenal gland in 1 patient. Prophylactic cranial irradiation (median dose, 30 Gy; range, 30-36 Gy) was given to 13 patients in 2-Gy fractions

Toxicity to High-Dose Therapy

Toxicity of therapy (Table 2) has been previously summarized in 2 of the individual studies [18,19]. Etanidazole proved overly toxic to the liver, kidneys, and peripheral nerves when combined with high-dose chemotherapy. Four patients died of toxicity (11%); death was due to renal failure in 2 patients, *Candida* infection in the third patient, and *Clostridium difficile* infection in the fourth patient.

Median times to granulocyte count ≥500/μL and platelet count ≥20,000/μL were 11 days (range, 8-33 days) and 18 days (range, 6-44 days), respectively. Patients who received PBPCs (n = 28) with or without marrow support recovered granulocytes (median of 10 days versus 29 days to granulocyte count ≥500/μL; $P = .006$) and platelets (median of 16 days versus 29 days to platelet count ≥20,000/μL; $P = .026$) more quickly than those who received marrow alone (n = 8). Platelet reconstitution was faster for patients who received chemotherapy/G-CSF–mobilized PBPCs than for those who received G-CSF– or GM-CSF–mobilized PBPCs (median of 10 days versus 20 days; $P = .01$). Patients underwent transfusion with a median of 10 units (range, 2-33 units) of packed RBCs and a median of 70 units (range, 0-292 units) of platelets. Two patients had severe alloimmunization resulting in refractory thrombocytopenia associated with bleeding. Acutely, all patients required antibiotics for support of fever during neutropenia.

Nonhematologic toxicities of the CBP and ICE regimens are compared in Table 2. Interstitial pneumonitis and grade 3 and 4 ototoxicity were more commonly seen following treatment with CBP; mucositis and elevations in AST, bilirubin, and creatinine levels were more commonly seen following treatment with ICE. These observations are consistent with the phase I/II literature concerning these regimens. Interstitial pneumonitis related to BCNU is reversible in large part with prednisone 1 mg/kg followed by a gradual taper over 6 to 8 weeks. These patients received

Table 2. *Nonhematologic Toxicity of CBP and ICE Regimens*

	CBP	ICE	P*
Patients	13	23	
Death within 90 days†	1	3	NS
Line infections	4	6	NS
Reversible congestive heart failure	1	1	NS
Interstitial pneumonitis requiring steroids	4	0	.04
Creatinine median, mg/dL	1.3	1.5	NS
Creatinine mean, mg/dL	1.59	3.26	.027
Ototoxicity (grade 3-4)	9	7	.035
AST (grade 3-4)	0	8	.002
Bilirubin (grade 3-4)	2	8	.17
Mucositis (grade 3-4)	1	10	.008

*Two-tailed *t* test.

†*Candida* sepsis, renal failure (n = 2), *Clostridium difficile*.

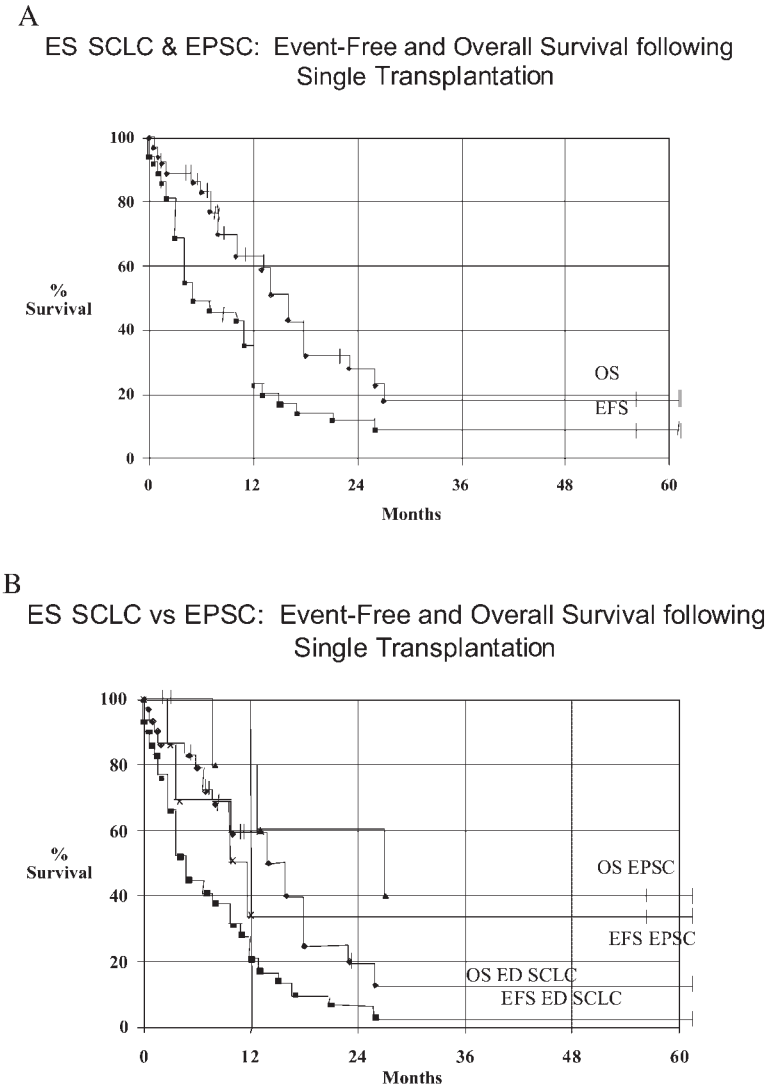

Figure 2. Overall survival (OS): time from initiation of high-dose chemotherapy to death from any cause; and event-free survival: time from initiation of high-dose chemotherapy to first failure (progression of disease or death from other causes) determined by Kaplan-Meier method. A, EFS and OS for all patients (n = 36), from day 1 of transplantation. B, EFS and OS of ES SCLC patients (n = 29), from day 1 of transplantation; EFS and OS for EPSC patients (n = 7), from day 1 of transplantation. (/) indicates follow-up time for patients.

prophylactic acyclovir and trimethoprim sulfazoxasole. Typhlitis and pneumonia occurred during the transplantation course in 2 and 3 patients, respectively. One patient developed transient hemolytic uremic syndrome 7 months post-CBP treatment.

Response to High-Dose Chemotherapy

Of 36 patients, 19 (53%) were not evaluable for response to high-dose chemotherapy (6 were in CR, 9 were in near-CR, and 4 died of treatment-related toxicity). Of 17 patients evaluable for response, the overall PR-to–CR/near-CR conversion rate was 53%. Two patients progressed with carcinomatous meningitis during the high-dose cycle on day +5.

Time to Failure and Relapse

The median times to failure from initiation of induction chemotherapy and after high-dose therapy for all patients were 12 and 5 months, respectively (Figure 2). All 6 patients who achieved ≤PR prior to high-dose therapy relapsed in a median of 3 months (range, 0.2-12 months). For all patients (n = 36), the 1-, 2-, and 5-year relapse-free survival was 24% (95% CI, 14%-44%), 12% (95% CI, 5%-31%), and 9% (95% CI, 3%-27%). The median event-free survival (EFS) for EPSC was 6 months (95% CI, 4-10 months). The median time from relapse to death was 3 months (range, 0-65 months). Sites of relapse were predominantly in unirradiated prior sites of disease. Five patients (2 SCLC, 3 EPSC) remained in continuous remission for a median of 55 months (range, 1-96 months). Four patients were progression free with follow-up more than 24 months following transplantation (2 SCLC, 2 EPSC). Three patients remained progression free long-term: 1 EPSC patient (parotid primary) had only local nodal metastases, and the other (colon primary) had diffuse liver disease; 1 SCLC patient had T3N3 plus

Table 3. *Favorable Prognostic Factors: Cox Regression Analysis*

Factor		Progression-Free Survival	Overall Survival
Histology	**EPSC versus SCLC**	***P* = .02**	***P* = .006**
Induction regimen	**ICE versus no ICE**	***P* = .03**	***P* = .009**
Induction duration	**≤4 versus >4 cycles**	***P* = .10**	***P* = .009**
Age	**≤50 years versus >50 years**	***P* = .13**	***P* = .05**
Response to induction	**CR/near-CR versus PR**	***P* = .26**	***P* = .09**

contralateral lung metastasis. One SCLC patient with TxN3 and 3 to 4 foci of bone disease relapsed with SCLC at 26 months and lived a total of 91 months.

Survival

The median survival times from initiation of induction chemotherapy and after high-dose therapy for all patients were 23 and 18 months, respectively (Figure 2). Thirteen patients remained alive with a median follow-up of 7 months (range, 1-96 months) after high-dose therapy. After intensification the probability of survival at 1 year was 61% (95% CI, 45%-81%), at 2 years was 28% (95% CI, 15%-52%), and at 5 years was 19% (95% CI, 8%-43%).

Cox Regression Analysis

The following factors were analyzed for survival and progression-free survival after high-dose chemotherapy: age (<50 versus >50), sex, EPSC versus SCLC, number of organs involved (1-2 versus 3 versus >3), number of cycles of induction (≤4 versus >4), months of induction, the degree of response to induction chemotherapy (CR/near-CR versus ≤PR), regimen (CBP versus ICE, for SCLC only), thoracic radiation therapy given (yes versus no), performance status at diagnosis (0 versus 1-4), and weight loss >5% at diagnosis (yes versus no) (Table 3). Factors associated with more favorable rates of EFS were the use of a more aggressive induction regimen (ICE; $P = .03$) and the EPSC histology ($P = .02$). Factors associated with more favorable overall survival included these 2 factors ($P = .009$ and .006, respectively) and also the use of short induction (≤4 cycles, $P = .009$) and younger age (<50 years, $P = .05$).

DISCUSSION

Higher rates of overall survival and CR are achieved by high-dose therapy than by conventional-dose therapy for a variety of hematologic and epithelial malignancies. In some malignancies, such as breast cancer, a dose-survival advantage of about 10% absolute has been suggested by promising results in phase II trials, although the phase III studies large enough to detect this degree of benefit are either not yet mature enough or have not yet been completed. In other malignancies, such as multiple myeloma and certain subsets of lymphoma, high-dose therapy with autologous hematopoietic support does provide a modest survival advantage in randomized trials. A small randomized trial in SCLC comparing conventional therapy to high-dose intensification proved the principle but resulted in an unacceptable 18% mortality [13]. A number of other phase I/II high-dose trials in SCLC have produced enhanced CR rates without obvious long-term survival benefit, particularly given patient selection biases and the high morbidity of treatment [24]. We have recently published our long-term follow-up results for patients with limited-stage SCLC responding to first-line therapy. Those near or in CR had a 53% 5-year EFS [25]. Although these outcomes should encourage further evaluation of this approach for the treatment of limited-stage SCLC, selection bias may have contributed to the favorable results; randomized studies remain a priority but are proving difficult to mount or complete.

In this study, we were able to deliver high-dose combined alkylating-agent therapy relatively safely, consistent with the substantial decline in the morbidity and mortality from high-dose chemotherapy with the development of PBPCs and hematopoietic cytokines. As a result, over the past 5 years, the upper age range of transplantation candidates has increased from 50 years to 65 years. It is noteworthy in the present study that, due in part to their nonsmoking status, patients with EPSC experienced lower morbidity and mortality and higher rates of survival than did ES SCLC patients ($P = .009$).

For a selected group of ES SCLC patients, we report 12% and 28% 2-year EFS and overall survival rates, respectively. Although the 2-year survival rate compares favorably with that for conventional-dose therapies in treatment of ES SCLC, selection biases favoring our patients, including younger age, a relative lack of comorbid disease, the insistence that they cease smoking, and tolerance to and excellent response to induction therapy, are probable contributors for this positive result. Further investigation using high-dose therapy in ES SCLC should focus on multicycle non–cross-resistant high-dose approaches rather than a single cycle of "late intensification" in the attempt to improve outcome. On the other hand, of the 7 patients with EPSC, 4 remained alive and 3 were relapse free at the time of this report. Given the expected poor prognosis for these patients, further phase II study is warranted in this subgroup.

Based on our observations, several other strategies could be explored to try to improve results: shorter initial therapy and earlier intensification, double transplantation, support with purged/selected stem cells, and the development of non–cross-resistant immunologic therapy targeting minimal disease. Earlier intensification of induction may improve overall disease-free and overall survival rates [26]. Multicycle dose-intensive combination therapies supported by cytokines and PBPCs represent logical promising treatment concepts [16,27,28]. Whether involved-field radiotherapy is beneficial in oligometastatic disease is unclear.

Stem cell contamination with tumor cells surviving induction therapy may be a source of relapse. As has been reviewed elsewhere, bone marrow is frequently involved in SCLC [29-33]. Early intensification using stem cell support

derived from untreated or post–first-cycle therapy may have a high rate of tumor contamination [34]. Even after achieving CR to chemotherapy, a high rate of residual contamination is observed [35-38]. Thus, stem cell selection may further enhance outcome. More importantly, these residual cells may represent a distinct subpopulation of tumor cells with identifiable biological features that confer not only drug-resistance phenotypes but perhaps also tumor stem cell properties.

High-dose therapy for ES SCLC should only be performed in the context of a clinical investigation and should focus on highly selected individuals with oligometastatic disease in excellent primary response or at the time of initial presentation. Further phase II experience in the consolidation of chemoresponsive disease for EPSC is warranted.

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